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ORIGINAL RESEARCH

Treatment-related adverse effects with pazopanib, sorafenib and sunitinib in patients with advanced soft tissue sarcoma: a pooled analysis

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Objective: Research efforts have investigated therapies targeting tyrosine kinase signaling pathways. We performed a pooled analysis to determine the frequency of severe adverse effects in patients with soft tissue sarcoma treated with pazopanib, sorafenib and sunitinib.

Materials and methods: We performed a comprehensive search of PubMed, Web of Science, Ovid, the Cochrane Library and Embase databases from the drugs' inception to May 2017 to identify clinical trials. All-grade and severe adverse events (AEs; grade≥3) were analyzed.

Results: A total of 10 trials published between 2009 and 2016, including 843 patients, were eligible for analysis. We included 424 patients (three studies) who received pazopanib 800 mg daily, 353 patients (five studies) who received sorafenib 400 mg twice daily and 66 patients (two studies) who received sunitinib 37.5 mg daily. The incidence of AEs is different among the three VEGFR-tyrosine kinase inhibitors (TKIs). Pazopanib showed higher incidence of all-grade nausea, diarrhea and hypertension compared with sorafenib and sunitinib. However, patients in the sorafenib group experienced a significantly higher frequency of all-grade rash (26.1%), hand–foot syndrome (33.4%) and mucositis (38.5%). The difference was highly significant for sorafenib vs. pazopanib in the incidence of all-grade rash (odds ratio [OR] 1.649, 95% CI 1.086–2.505, P=0.023), hand–foot syndrome (OR 3.096, 95% CI 1.271–7.544, P=0.009) and mucositis (OR 4.562, 95% CI 2.132–9.609, P<0.001). Moreover, the frequency of grade ≥3 mucositis was significantly higher in the sunitinib group compared with the pazopanib or sorafenib group (7.6% vs. 1.3%, OR 6.448, 95% CI 1.499–27.731, P=0.013).

Conclusion: Statistically significant differences in certain common adverse effects, such as all-grade and severe AEs, were detected among pazopanib, sorafenib and sunitinib in the current study. Early and prompt management is critically needed to avoid unnecessary dose reductions and treatment-related discontinuations.

Keywords: pazopanib, sorafenib, sunitinib, soft tissue sarcoma

Introduction

Soft tissue sarcomas (STSs) are a group of rare mesenchymal cancers that include approximately 50 histological subtypes and comprise approximately 1% of all adult cancers.[1,2] Surgery with or without radiotherapy is the primary treatment for early-stage localized STS.[3,4] The conventional treatment for patients with inoperable or metastatic STSs is an anthracycline (usually doxorubicin), either as a monotherapy or in combination with ifofamide.[5] However, the prognosis of metastatic or advanced STS is poor.

Given the need for improved therapies, investigations into novel treatments for advanced STS are continuing. Recently, studies have been performed to test

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anti-angiogenic treatment, and efforts have been focused on therapies targeting tyrosine kinase signaling pathways.[6–8] The small molecule vascular endothelial growth factor inhibitor, pazopanib, is a multi-targeted tyrosine kinase inhibitor (TKI) with high affinity against VEGFR-1/2/3 and with a lower affinity against PDGFR-α/β, FGFR-1/2 and stem cell factor receptor (c-KitR).[9] Based on the clinical trials, pazopanib was determined to be well tolerated in metastatic or advanced STS and demonstrated antitumor activity in non-liposarcoma.[10,11] Therefore, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved pazopanib for the treatment of advanced STS in those who have received prior chemotherapy.[12]

Sorafenib, also a small molecule B-raf and VEGFR inhibitor, is potentially useful in several specific sarcoma subtypes, such as angiosarcomas.[13] Moreover, sorafenib in patients with solid tumors indicated a promising 30% PFR_{12} in patients with metastatic sarcomas.[14] Furthermore, in malignant peripheral nerve sheath tumours (MPNSTs) with the loss of NF1 and the activation of the ras–raf signaling pathway,[15–17] sorafenib demonstrated activity. Based on preclinical data, the level of tumor growth inhibition for pazopanib was similar to that for sorafenib.[18–20]

Sunitinib is also a multi-targeted TKI with activity against VEGFRs1/2/3, PDGFR-α/β, KIT, FLT3, RET and CSF-1.[21] The role of sunitinib has also been extensively studied in STS. Furthermore, clinical efficacy has been indicated in patients with advanced STS, predominantly in liposarcomas, leimyosarcomas,[22] solitary fibrous tumors[23] and alveolar STSs.[24]

In the past decade, three TKIs have been developed as angiogenesis inhibitors and showed their antitumor response in several solid tumors.[10,25–29] However, the use of VEGFR-TKIs is limited by their different side effects, in which the precise underlying mechanism often remains unclear. The difference in the toxicity pattern among pazopanib, sunitinib and sorafenib remains unclear.[30] Although pazopanib is the only one which has been approved by the FDA for patients with sarcoma, sunitinib and sorafenib have shown definite efficacy in some specific types of sarcomas. There is a great potential for TKIs in the treatment of patients with sarcoma. Notably, the three TKIs show a promising response rate in STS. Compliance with anticancer therapy is determined by their tolerability. Therefore, it is important to choose optimal TKIs by performing a pooled analysis of the occurrence of adverse events (AEs) based on data extracted from clinical trials of patients with STS.

Materials and methods

Study identification

The following computerized databases were used to search the relevant literature for clinical trials: PubMed, Web of Science, Ovid, the Cochrane Library and Embase, encompassing the period from the drugs' inception to May 2017. The search keywords were "pazopanib," "sunitinib," "sorafenib," and "sarcoma." Abstracts from American Society of Clinical Oncology (ASCO) meetings were hand searched to scan for updated data and to identify new studies. In addition, duplicate data were removed, and the articles were screened to determine whether the article was relevant. Duplicate research or irrelevant articles were discarded after retrieval and review. Reference lists were also hand searched to identify any additional articles.

The study's inclusion criteria were as follows: 1) patients ≥18 years or older with metastatic or locally advanced STS (non-GISTs); 2) intervention: pazopanib, sunitinib or sorafenib, not combined with other therapies; 3) sufficient data presented on treatment-related AEs (TRAEs), including all information about all-grade and grade ≥3 toxicity and 4) written in English. All case reports, letters, commentaries and reviews were excluded.

Data extraction and quality control

The first author's name, publication year, therapeutic drug (pazopanib, sunitinib or sorafenib), number of patients evaluable for all-grade and grade ≥3 toxicity (nausea, diarrhea, fatigue, vomiting, hypertension, hand–foot syndrome, rash, elevated ALT, neutropenia, leukopenia and anemia, mucositis, number of patients experiencing treatment-related death [TRD] and withdrawal resulting from severe toxicity) were evaluated. Clinical trials were collected for patients receiving pazopanib 800 mg daily, sorafenib 400 mg twice daily and sunitinib 37.5 mg daily according to the FDA-recommended dose. Two studies including patients receiving sunitinib 50 mg daily were excluded.[22,31] Studies were independently selected by two authors based on the aforementioned inclusion criteria.

The full texts of nonrandomized clinical trials were assessed using the 9-point Newcastle–Ottawa Scale (NOS). Two investigators evaluated the studies independently. Studies were categorized into three broad perspectives, including selection, comparability and outcome for cohort studies or exposure for case–control studies. A score of 7 or greater was considered to be high quality. The risk of bias in the included studies was independently assessed by two investigators using

the Cochrane Collaboration's tool for assessing the risk of bias in randomized controlled trials (RCTs).[32] Two authors independently assessed each study under five main headings for the risk of bias.

Statistical analyses

All statistical analyses were performed using GraphPad Prism software (version 6.0; GraphPad Software, Inc., La Jolla, CA, USA). Fisher's exact or chi-square tests were used to compare the frequencies of AEs among three multiple receptor tyrosine kinases. All tests were two tailed, and statistical significance was considered at $P<0.05$.

Results

Characteristics of the original selected studies

Based on our inclusion criteria, 10 clinical trials were identified to address multiple receptor tyrosine kinase-treated STSs (Figure 1). Among the 10 trials published between 2009 and 2016, 843 patients with STS were eligible for the current study. The sample size of the eligible trials ranged from 14 to 239. We included 424 patients (three studies)[10,11,33] who received pazopanib, 353 patients (five studies)[13,34–37] who received sorafenib and 66 patients (two studies)[38,39] who received sunitinib. All the patients received the multiple TKI alone. The primary characteristics of the included trials are listed in Table 1.

Study quality assessment and risk of bias

The methodological quality of all non-RCTs (NRCTs; excluding abstracts and conference abstracts) is listed in Table S1. No major flaws of the included RCTs were detected in assessing their risk of bias (Table S2). However, the expected absence of a blinded intervention was a common caveat.

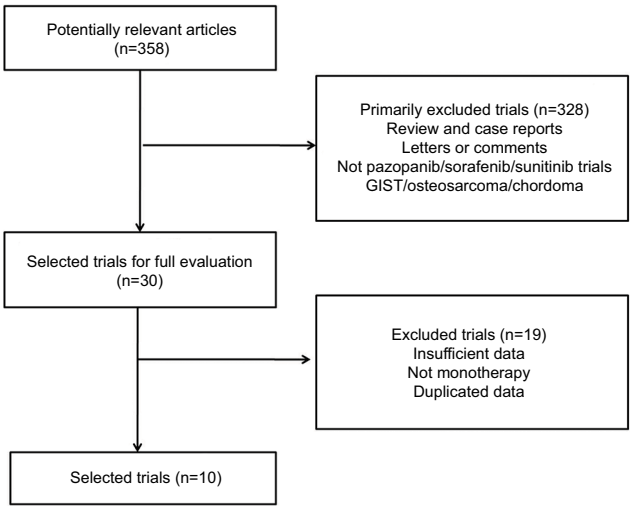

Figure 1 Flow diagram of selection of trials included in the pooled analysis.

Frequency of all-grade TRAEs between different VEGFR-TKI types

We analyzed the incidence and odds ratio (OR) of TRAEs by VEGFR-TKI in patients with STS. The incidence of all-grade nausea was highest with pazopanib (47.2%) followed by sunitinib (24.2%) and sorafenib (7.6%). The difference between incidence was highly significant for pazopanib vs. sunitinib (OR 2.799, 95% CI 1.539–5.088, $P<0.001$), sunitinib vs. sorafenib (OR 3.865, 95% CI 1.740–8.584, $P=0.001$) and pazopanib vs. sorafenib (OR 10.815, 95% CI 5.933–19.713, $P<0.001$; Figure 2A).

A similar pattern was observed in the frequency of all-grade hypertension. The incidence of all-grade hypertension was highest with pazopanib (40.9%) followed by sunitinib (18.2%) and sorafenib (9.3%). The difference between the incidences was highly significant for pazopanib vs. sorafenib (OR 6.723, 95% CI 4.451–10.155, $P<0.001$), sunitinib vs. sorafenib (OR 2.155, 95% CI 1.048–4.431, $P=0.049$) and pazopanib vs. sunitinib (OR 3.120, 95% CI 1.616–6.024, $P<0.001$; Figure 2B).

For all-grade fatigue, the frequency was 54.3% for pazopanib, 45.5% for sunitinib and 30.0% for sorafenib. Significant differences were found between pazopanib vs. sorafenib (OR 2.772, 95% CI 2.045–3.757, $P<0.001$). Meanwhile, patients in the sunitinib group experienced significantly higher frequency of all-grade fatigue than patients in the sorafenib group (OR 1.942, 95% CI 1.137–3.317, $P=0.021$), whereas the difference between pazopanib vs. sunitinib was not significant (OR 1.428, 95% CI 0.845–2.413, $P=0.185$; Figure 2C).

Similarly, the frequency of all-grade diarrhea was significantly greater in patients treated with pazopanib than in those treated with sorafenib (43.2% vs. 23.5%, OR 2.470, 95% CI 1.808–3.375, $P<0.001$). Moreover, statistical significance was observed between the sunitinib and sorafenib groups (42.4% vs. 23.5% OR 2.397, 95% CI 1.388–4.141, $P=0.002$), Nonetheless, there was no significant difference between the pazopanib and sunitinib cohort (43.2% vs. 42.4%, OR 1.031, 95% CI 0.610–1.741, $P=1.000$; Figure 2D).

All-grade vomiting was significantly more common for pazopanib compared with sorafenib (27.4% vs. 5.4%, OR 6.183, 95% CI 3.324–11.501, $P<0.001$). However, statistical significance was not observed between the sorafenib and sunitinib groups (5.4% vs. 7.1%, OR 0.792, 95% CI

Table 1 Baseline characteristics of trials included in the pooled analysis

Study	Year	Treatment	Number of patients evaluated for toxicity	Number of patients experienced toxicity (grade ≥3)/all-grade			
				Nausea	Fatigue	Diarrhea	Vomiting
Sleijfer et al[11]	2009	Pazopanib	142	1/51	11/52	5/43	NA/34
van der Graaf et al[10]	2012	Pazopanib	239	8/129	31/155	11/138	8/80
Yoo et al[33]	2015	Pazopanib	43	NA	NA	2/2	2/2
Maki et al[13]	2009	Sorafenib	144	NA	9/23	4/10	NA
von Mehren et al[34]	2012	Sorafenib	37	1/1	2/24	4/22	1/1
Ray-Coquard et al[35]	2011	Sorafenib	39	NA	6/12	6/13	0/4
Santoro et al[36]	2013	Sorafenib	100	2/6	5/39	7/27	0/6
Bramswig et al[37]	2014	Sorafenib	33	3/6	1/8	1/11	0/1
George et al[38]	2009	Sunitinib	52	0/14	1/27	3/25	NA
Li et al[39]	2016	Sunitinib	14	0/2	0/3	0/3	0/1

Abbreviation: NA, not available.

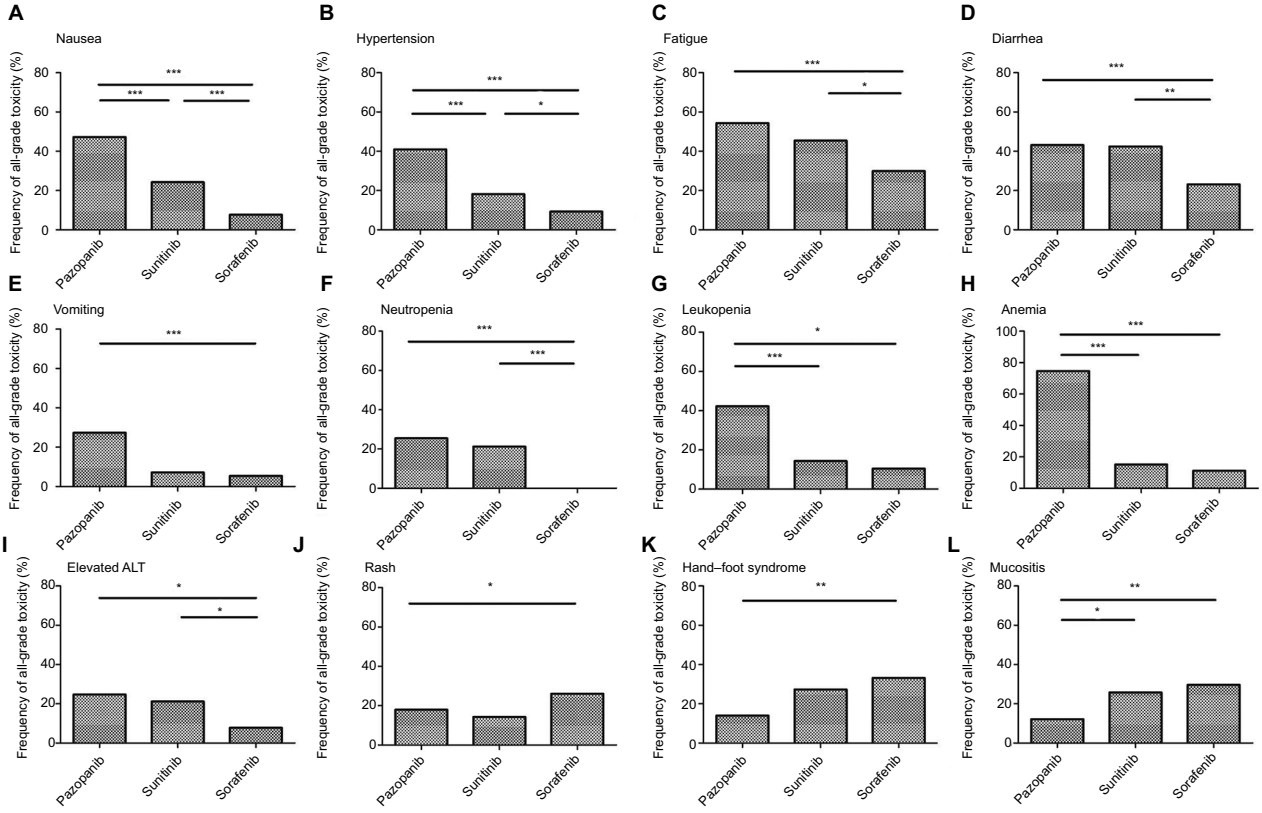

Figure 2 Frequency of all-grade toxicity, including nausea (**A**), hypertension (**B**), fatigue (**C**), diarrhea (**D**), vomiting (**E**), neutropenia (**F**), leukopenia (**G**), anemia (**H**), elevated ALT (**I**), rash (**J**), hand–foot syndrome (**K**) and mucositis (**L**) among different multiple TKIs.
Note: *p<0.05, **p<0.01 and ***p<0.001 indicate statistically significant differences.
Abbreviations: ALT, alanine aminotransferase; TKIs, tyrosine kinase inhibitors.

0.095–6.570, P=0.580). In addition, there was no significant difference between pazopanib and sunitinib (27.4% vs. 7.1%, OR 4.896, 95% CI 0.633–37.848, P=0.126; Figure 2E).

The frequency of all-grade neutropenia differed significantly between pazopanib and sorafenib (25.4% vs. 0.0%, OR 1.283, 95% CI 1.186–1.387, P<0.001). Statistical significance was also observed between sunitinib and sorafenib (21.2% vs. 0.0%, OR 1.750, 95% CI 1.465–2.091, P=0.002). However, there was no significant difference between pazopanib and sunitinib (25.4% vs. 21.2%, OR 1.265, 95% CI 0.643–2.489, P=0.616; Figure 2F). For all-grade leukopenia, patients in the pazopanib group also experienced significantly higher frequency than patients

Hypertension	Rash	Mucositis	Anemia	Hand–foot syndrome	Increased alanine transaminase	Neutropenia	Leukopenia
11/57	NA	NA	6/106	NA	6/71	6/45	2/60
16/99	1/43	3/29	NA	NA	NA/23	NA	NA
NA	NA	NA	NA	NA/6	NA	2/2	NA
6/15	17/28	NA	NA	18/47	3/13	NA	4/15
2/2	2/2	NA	NA	4/25	NA/1	NA	NA
1/3	NA	2/15	3/5	6/11	NA	0/0	NA
0/7	4/42	NA	NA	4/28	NA	NA	NA
3/6	3/10	NA	NA	2/7	NA	NA	NA
1/11	NA	5/12	3/8	4/15	3/11	2/13	NA
0/1	0/2	0/5	1/2	1/3	NA	0/1	0/2

in the sorafenib group (42.3% vs. 10.4%, OR 6.293, 95% CI 3.352–11.814, $P<0.001$) and sunitinib group (42.3% vs. 14.3%, OR 4.390, 95% CI 0.947–20.347, $P=0.048$), whereas there was no significant difference between sunitinib and sorafenib (14.3% vs. 10.4%, OR 1.433, 95% CI 0.292–7.026, $P=0.649$; Figure 2G). A similar pattern was observed in the frequency of all-grade anemia between pazopanib and sorafenib (74.6% vs. 12.8%, OR 20.022, 95% CI 7.278–55.085, $P<0.001$) and pazopanib and sunitinib (74.6% vs. 15.2%, OR 16.489, 95% CI 7.621–35.677, $P<0.001$), Nonetheless, there was no significant difference between the sunitinib and sorafenib groups (15.2% vs. 12.8%, OR 1.214, 95% CI 0.383–3.854, $P=1.000$; Figure 2H).

Another common adverse effect, elevated all-grade ALT, was more common for pazopanib compared with sorafenib (24.7% vs. 7.7%, OR 3.907, 95% CI 2.159–7.069, $P<0.001$) and sunitinib vs. sorafenib (21.2% vs. 7.7%, OR 3.200, 95% CI 1.354–7.566, $P=0.010$). Statistical significance was not observed between pazopanib and sunitinib (24.7% vs. 21.2%, OR 1.221, 95% CI 0.603–2.471, $P=0.730$; Figure 2I).

A further analysis of common skin and mucosa dysfunctions (rash, hand–foot syndrome and mucositis) was conducted among the three VEGFR-TKI types. Patients in the sorafenib group experienced a significantly higher frequency of all-grade rash (26.1%), hand–foot syndrome (33.4%) and mucositis (38.5%). The difference was highly significant for sorafenib vs. pazopanib for the incidence of all-grade rash (OR 1.649, 95% CI 1.086–2.505, $P=0.023$; Figure 2J), hand–foot syndrome (OR 3.096, 95% CI 1.271–7.544, $P=0.009$; Figure 2K) and mucositis (OR 4.562, 95% CI 2.132–9.609, $P<0.001$; Figure 2L).

Frequency of severe TRAEs (grade ≥3) between different VEGFR-TKI types

Grade ≥3 fatigue was significantly more common for pazopanib compared with sorafenib (11.0% vs. 6.5%, OR 1.778, 95% CI 1.046–3.022, $P=0.037$) and sunitinib (11.0% vs. 1.5%, OR 8.053, 95% CI 1.089–59.555, $P=0.012$). Nonetheless, there was no significant difference between the sorafenib and sunitinib cohorts (6.5% vs. 1.5%, OR 4.530, 95% CI 0.601–34.141, $P=0.149$; Figure 3A).

A similar pattern was observed in the frequency of grade ≥3 vomiting in the pazopanib vs. sorafenib groups (3.5% vs. 0.5%, OR 7.647, 95% CI 0.971–60.211, $P=0.028$), whereas there was no significant difference between pazopanib and sunitinib (3.5% vs. 0.0%, OR 1.051, 95% CI 1.024–1.079, $P=1.000$) or sorafenib and sunitinib (0.5% vs. 0.0%, OR 1.067, 95% CI 1.031–1.104, $P=1.000$; Figure 3B).

Patients in the pazopanib group experienced a significantly higher frequency of severe hypertension than patients in the sorafenib group (7.1% vs. 3.4%, OR 2.143, 95% CI 1.069–4.298, $P=0.032$). However, the frequency of grade ≥3 hypertension did not differ significantly between the pazopanib and sunitinib groups (7.1% vs. 1.5%, OR 4.902, 95% CI 0.655–36.710, $P=0.101$). Moreover, statistical significance was not observed between the sorafenib and sunitinib groups (3.4% vs. 1.5%, OR 2.287, 95% CI 0.292–17.896, $P=0.702$; Figure 3C).

Another common adverse effect, grade ≥3 rash, was less common for pazopanib compared with sorafenib (0.4% vs. 8.3%, OR 0.047, 95% CI 0.006–0.346, $P<0.001$). Statistical significance was not observed between pazopanib and sunitinib (0.4% vs. 0.0%, OR 1.059, 95% CI 1.028–1.091, $P=1.000$); likewise, it was not observed between sorafenib

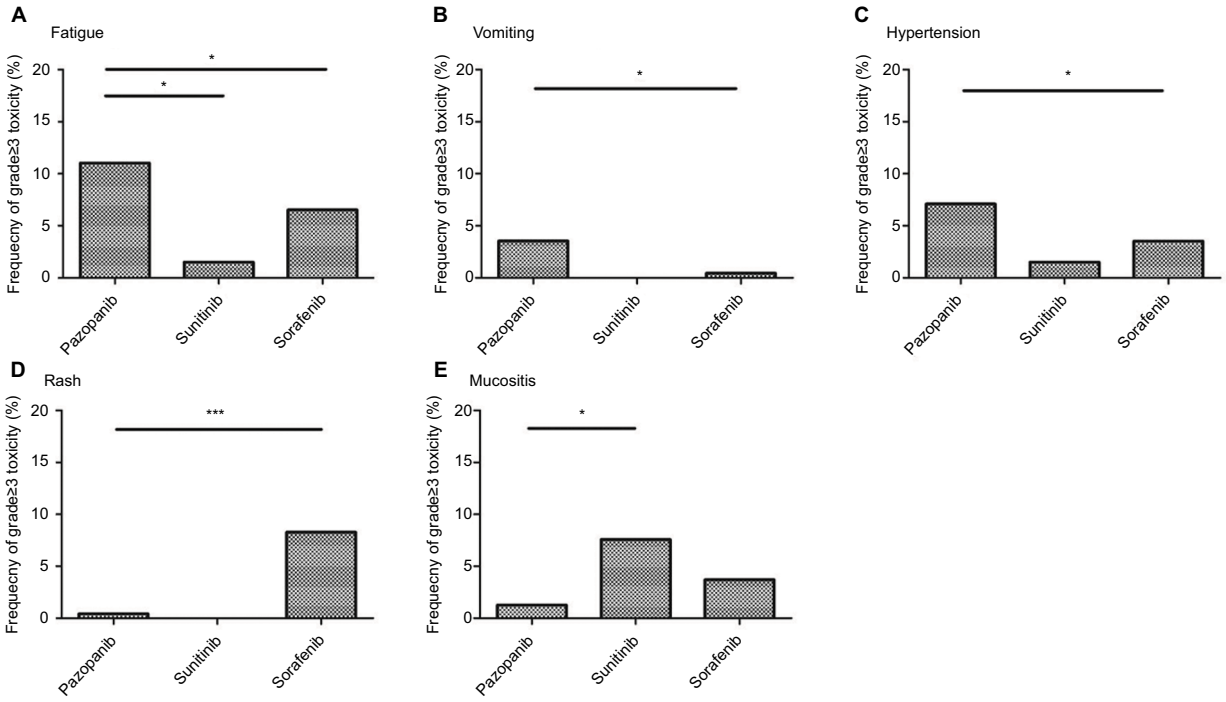

Figure 3 Frequency of AEs, grade≥3, including fatigue (**A**), vomiting (**B**), hypertension (**C**), rash (**D**) and mucositis (**E**) among different multiple TKIs.
Note: *$p<0.05$ and ***$p<0.001$ indicate statistically significant differences.
Abbreviations: AEs, adverse events; TKIs, tyrosine kinase inhibitors.

and sunitinib (8.3% vs. 0.0%, OR 1.049, 95% CI 1.023–1.075, P=0.613; Figure 3D).

For grade ≥3 mucositis, the frequency was highest with sunitinib (7.6%), followed by sorafenib (5.1%) and pazopanib (1.3%). Statistical significance was observed in investigating the frequency of mucositis grade ≥3 for sunitinib vs. pazopanib (7.6% vs. 1.3%, OR 6.448, 95% CI 1.499–27.731, P=0.013; Figure 3E).

As for grade ≥3 nausea, neutropenia, leukopenia, anemia, elevated ALT and hand–foot syndrome, no statistical significance was detected among all three cohorts (data not shown).

By pooled analysis, complete responses and partial responses were observed in 39 patients in the pazopanib group, 27 in the sorafenib group and five in the sunitinib group. Objective response rates were similar among the three groups (Table S3).

Identification of withdrawal toxicity and TRD for pazopanib vs. sorafenib

The overall frequency of AEs that resulted in treatment withdrawal for pazopanib and sorafenib was 11.1% (47 of 424 evaluable patients) and 11.0% (39 of 353 evaluable patients), respectively. No significant difference was observed among the two groups. However, a significant difference in AEs that resulted in TRD was observed between pazopanib and sorafenib (3.3% vs. 0.0, OR 1.620, 95% CI 1.480–1.733, P=0.029). The frequency of the overall TRD for pazopanib and sorafenib was 3.3% (eight of 239 evaluable patients) and 0.0% (zero of 139 evaluable patients), respectively.

Discussion

In the past decade, several small molecule TKIs, including pazopanib, sunitinib and sorafenib, have demonstrated clinical efficacy in STS.[10,11,13,36,38] However, the use of these inhibitors is limited by the occurrence of severe adverse effects, such as hypertension, rash and fatigue.[40,41] Treatments that alleviate and prevent side effects ultimately lead to enhanced health-related quality of life (HRQoL) of patients. The determination of frequency of TRAEs of different TKIs in STS may enable the early management of most susceptible patients. In this regard, there is a critical need to determine the frequency of AEs to reduce the risk of treatment-related withdrawal or death.

To the best of our knowledge, the current study is the first pooled analysis in STS, focusing on the differences in TRAEs among pazopanib, sunitinib and sorafenib. In our analysis, pazopanib had the highest incidence of all-grade nausea, fatigue, vomiting, diarrhea, hypertension, elevated alanine aminotransferase (ALT), neutropenia, leukopenia

and anemia compared with sorafenib and sunitinib; likewise, the frequency of grade ≥3 fatigue, vomiting and hypertension was also the highest in pazopanib-treated patients. We further observed that the frequency of AEs that resulted in TRD was significantly different between the pazopanib and sorafenib groups. Conversely, the frequency of rash, hand–foot syndrome and mucositis was highest in the sorafenib group compared with the pazopanib and sunitinib groups, and sorafenib-treated patients had the highest incidence of grade ≥3 rash among the three groups. Moreover, the frequency of grade ≥3 mucositis was significantly higher in the sunitinib group compared with the pazopanib or sorafenib groups.

A double-blind, randomized crossover study sought to assess the preference between sunitinib and pazopanib for patients with metastatic renal cell carcinoma (RCC).[42] This study observed that, for most of the AEs, especially fatigue, patients preferred pazopanib over sunitinib. In a meta-analysis, Santoni et al[43] demonstrated that sorafenib had a lower incidence of risk ratio (RR) of all-grade gastrointestinal (GI) events compared with pazopanib and sunitinib. However, these results have not focused on the STS subgroup. In addition, the differences in some common adverse effects of anti-angiogenesis, including rash, hand–foot syndrome and hypertension, among pazopanib, sunitinib and sorafenib, have not been determined. The different evaluation time points of adverse effects and different doses of TKIs in the studies may drive the different results. For example, in our article, we included patients who received pazopanib 800 mg daily and sunitinib 37.5 mg daily. However, Escudier et al[42] reported that patients with metastatic RCC were randomly assigned to pazopanib 800 mg/day for 10 weeks, a 2-week washout, and then sunitinib 50 mg/day (4 weeks on, 2 weeks off, 4 weeks on).

Imatinib mesylate is also a competitive inhibitor of tyrosine kinases selectively associated with c-Kit and platelet derived growth factor receptors.[44] Besides GIST, it has been registered for advanced/metastatic dermatofibrosarcoma protuberans (DFSPs). Two Phase II trials formally proved the activity of the drug in this disease, with a 50% overall response rate leading to the registration for this disease.[45,46] Similar activity has been shown in the rare fibrosarcomatous variant although with a more limited duration.[47,48] Imatinib is therefore currently used in classical locally advanced DFSP and in metastatic fibrosarcomatous DFSP. Given that the good clinical response and limited dose-related effect of imatinib in DFSP may to some extent influence the result, we did not include imatinib in the pooled analysis.

Our study has several limitations. First, this study analyzed all published clinical trials and determined the statistical significance of severe AEs among VEGFR-TKIs. However, the small number of patients receiving sunitinib compared with those receiving pazopanib or sorafenib may to some extent be a limitation. Thus, a large sample size of prospective RCTs is required. Second, a portion of AE information was not obtained, even though we contacted the corresponding authors. Third, the association between treatment-related toxicities and clinical outcome in patients with VEGFR-TKI still remains to be elucidated. Further studies are urgently needed to understand the underlying mechanism of this association.

Conclusion

Our study has shown that different VEGFR-TKIs are associated with a significantly increased risk of treatment-related toxicities. The prompt and early management of these events is critically needed to reduce their impact on patient outcome and quality of life (QoL) to optimize medical resource utilization. Therefore, physicians and patients should be aware of these risks when managing the use of these VEGFR-TKIs in STS.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Nine-point NOS scores for the NRCTs

Study	Selection (maximum of four stars)				Comparability (maximum of two stars)	Outcome (maximum of three stars)		
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration of the outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of the outcome	Was follow-up long enough for the outcome to occur	Adequacy of follow-up of cohorts
Sleijfer et al[1]			*	*		*	*	*
Yoo et al[2]			*	*		*	*	*
Maki et al[3]			*	*		*	*	*
von Mehren et al[4]			*	*		*	*	*
Ray-Coquard et al[5]			*	*		*	*	*
Santoro et al[6]			*	*		*	*	*
Bramswig et al[7]			*	*		*	*	*
George et al[8]			*	*		*	*	*
Li et al[9]			*	*		*	*	*

Notes: The NOS score is an easy, convenient tool for quality assessment of nonrandomized studies. *Based on three domains: selection of study groups; comparability of groups; ascertainment of exposure/outcome. No major flaws of the included RCTs were detected in assessing their risk of bias.

Abbreviations: NOS, Newcastle–Ottawa Scale; NRCTs, nonrandomized controlled trials.

Table S2 Risk of bias in RCTs

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free selective reporting	Free of other bias
van der Graaf et al[10]	Yes	Yes	Yes	No	No	No

Abbreviation: RCTs, randomized controlled trials.

Table S3 The clinical therapeutic effects of the included studies

Study	Treatment	Number of patients evaluated for efficacy	PR+CR (n)	SD+PD (n)
Sleijfer et al[1]	Pazopanib	138	9	NA
van der Graaf et al[10]	Pazopanib	246	23	221
Yoo et al[2]	Pazopanib	41	7	34
Maki et al[3]	Sorafenib	122	6	116
von Mehren et al[4]	Sorafenib	37	2	31
Ray-Coquard et al[5]	Sorafenib	41	4	29
Santoro et al[6]	Sorafenib	76	11	59
Bramswig et al[7]	Sorafenib	20	4	16
George et al[8]	Sunitinib	48	1	47
Li et al[9]	Sunitinib	14	4	10

Abbreviations: NA, not available; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

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